Answer 1:

Bibliographic Information

Androgen Receptor Blockade in Experimental Combination Therapy of Pancreatic Cancer. Konduri, Srivani; Schwarz, Margaret A.; Cafasso, Danielle; Schwarz, Roderich E. Department of Surgery, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, Divisions of Surgical Oncology and Surgical Sciences, The Cancer Institute of New Jersey, New Brunswick, NJ, USA. Journal of Surgical Research (2007), 142(2), 378-386. Publisher: Elsevier, CODEN: JSGRA2 ISSN: 0022-4804. Journal written in English. CAN 148:112427 AN 2007:1073190 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background: Reports on hormone receptor expression of pancreatic cancer (PaCa) cells and treatment responses to antihormonal therapy are still conflicting. Methods: Eight human PaCa cell lines were tested for androgen receptor (AR) protein levels by Western blot anal. Cell proliferation in vitro was measured by sulforhodamine B anal. AR agonists and inhibitors included dihydrotestosterone (DHT), testosterone (T), and flutamide (Flu). In vivo therapy of nude mouse xenografts tested Flu with gemcitabine (Gem) and/or bevacizumab (Bev). Results: Seven of eight human PaCa cell lines expressed detectable AR protein. Median relative expression compared with the AR pos. control LnCaP was 21% (range: 16 to 63). Growth stimulation by DHT or T was minor (<20%); inhibition by Flu varied greatly and did not correlate to AR levels. Even in the sensitive cell line Panc1, Flu failed to increase Gem toxicity in vitro. However, in vivo Flu therapy resulted in significant growth inhibition of Panc-1 tumors. Flu/Gem treatment did not enhance the effect; Bev/Flu/Gem triple therapy had the greatest effect (P = 0.06 compared to Flu/Gem). Flu alone did not affect apoptotic activity, but decreased the tumor cell proliferative index (P = 0.04); in combination with Gem, Flu reduced the tumor cell d. (P = 0.02). Conclusions: The majority of PaCa cell lines express AR at various levels, but most fail to show an in vitro antiproliferative response to AR inhibition. The strong antitumor effect of flutamide in vivo is not significantly enhanced in combination with gemcitabine or bevacizumab, suggesting primarily monotherapy benefit potential of AR blockade in susceptible PaCa.

Answer 2:

Bibliographic Information

Promotion of bladder cancer development and progression by androgen receptor signals. Miyamoto, Hiroshi; Yang, Zhiming; Chen, Yei-Tsung; Ishiguro, Hitoshi; Uemura, Hiroji; Kubota, Yoshinobu; Nagashima, Yoji; Chang, Yu-Jia; Hu, Yueh-Chiang; Tsai, Meng-Yin; Yeh, Shuyuan; Messing, Edward M.; Chang, Chawnshang. Departments of Pathology and Urology, University of Rochester Medical Center, Rochester, NY, USA. Journal of the National Cancer Institute (2007), 99(7), 558-568. Publisher: Oxford University Press, CODEN: JNCIEQ ISSN: 0027-8874. Journal written in English. CAN 147:320078 AN 2007:541304 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background: Males have a higher incidence of bladder cancer than females, but the reason remains unknown. Unlike prostate cancer, human bladder cancer is not generally considered to be dependent on hormone activity. We investigated the possible involvement of androgens and the androgen receptor (AR) in bladder cancer. Methods: We used N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) to induce bladder cancer in wild-type male and female mice, with and without castration in males, and in AR knockout (ARKO) male and female mice, with and without dihydrotestosterone (DHT) supplementation in males. We also treated human bladder cancer cell lines, including TCC-SUP and UMUC3, and mouse xenograft models established from these same lines with androgen deprivation therapy (antiandrogen treatment or castration), AR-small-interfering RNA (AR-siRNA), or the anti-AR mol. ASC-J9, which causes selective degrdn. of the AR. Results: More than 92% of wild-type male and 42% of wild-type female mice treated with BBN eventually developed bladder cancer, whereas none of the male or female ARKO mice did. Treatment with BBN induced bladder cancer in 25% of ARKO mice supplemented with DHT and in 50% of castrated wild-type male mice. Androgen deprivation of AR-pos. human bladder cancer cells by androgen depletion in vitro or castration in mice and/or by treatment with the antiandrogen flutamide in vitro or in vivo, as well as AR knockdown by AR-siRNA or by ASC-J9, suppressed cell proliferation in vitro and xenograft tumor growth in vivo. Conclusions: Our findings implicate the involvement of both androgens and the AR in bladder cancer. Targeting AR and androgens may provide novel chemopreventive and therapeutic approaches for bladder cancer.

Answer 3:

Bibliographic Information

Par-4-dependent apoptosis by the dietary compound. withaferin A in prostate cancer cells. Srinivasan, Sowmyalakshmi; Ranga, Rama S.; Burikhanov, Ravshan; Han, Seong-Su; Chendil, Damodaran. Departments of Clinical Sciences, College of Health Sciences and Radiation Medicine, College of Medicine, University of Kentucky, Lexington, KY, USA. Cancer Research (2006), Volume Date 2007, 67(1), 246-253. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 146:134906 AN 2007:25050 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Deletion or mutation of the androgen receptor (AR) renders prostate tumors refractory to apoptosis by androgen ablation, the mainstay of prostate cancer therapy. To identify novel therapeutics that can induce apoptosis regardless of the AR status of prostate cancer cells, we screened dietary herbal compds. using a reporter assay for the prostate apoptosis response-4 (Par-4) gene, which induces p53- and PTEN-independent and cancer-selective apoptosis. One of the compds., withaferin A (WA), a major constituent of the dietary compound. Withania somnifera, induced Par-4-dependent apoptosis in androgen-refractory prostate cancer cells and regression of PC-3 xenografts in nude mice. Interestingly, restoration of wild-type AR in PC-3 (AR neg.) cells abrogated both Par-4 induction and apoptosis by WA. Individually, WA and anti-androgens induced neither Par-4 nor apoptosis in androgen-responsive prostate cancer cells, yet in combination, WA and anti-androgen synergistically induced Par-4 and apoptosis in androgen-responsive prostate cancer cells. Thus, when judiciously combined with anti-androgens, WA inhibits survival of both androgen-responsive and androgen-refractory prostate cancer cells by a Par-4-dependent mechanism. As Par-4 up-regulation induces apoptosis in most tumor cells, our findings can be extended to high-throughput screens to identify synergistic combinations for both therapy-sensitive and therapy-resistant cancers.

Answer 4:

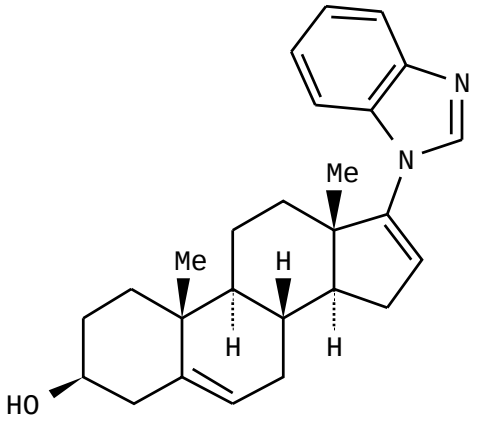
Bibliographic Information

Novel C-17-Heteroaryl Steroidal CYP17 Inhibitors/Antiandrogens: Synthesis, in Vitro Biological Activity, Pharmacokinetics, and Antitumor Activity in the LAPC4 Human Prostate Cancer Xenograft Model. Handratta, Venkatesh D.; Vasaitis, Tadas S.; Njar, Vincent C. O.; Gediya, Lalji K.; Kataria, Ritesh; Chopra, Pankaj; Newman, Donnell, Jr.; Farquhar, Rena; Guo, Zhiyong; Qiu, Yun; Brodie, Angela M. H. Department of Pharmacology and Experimental Therapeutics, University of Maryland School of Medicine, Baltimore, MD, USA. Journal of Medicinal Chemistry (2005), 48(8), 2972-2984. Publisher: American Chemical Society, CODEN: JMCMAR ISSN: 0022-2623. Journal written in English. CAN 142:482186 AN 2005:267013 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

New chem. entities, steroidal C-17 benzoazoles and pyrazines were rationally designed and synthesized. The key reaction for synthesis of the benzoazoles involved the nucleophilic vinylic "addn.-elimination" substitution reaction of 3β-acetoxy-17-chloro-16-formylandrosta-5,16-diene and benzoazole nucleophiles, while that for synthesis of pyrazines involved palladium-catalyzed cross-coupling reaction of 17-iodoandrosta-5,16-dien-3β-ol with tributylstannyl diazines. Some of the compds. were shown to be potent inhibitors of human CYP17 enzyme as well as potent antagonist of both wild type and mutant androgen receptors (AR). The most potent CYP17 inhibitors were 3β-hydroxy-17-(1H-benzimidazol-1-yl)androsta-5,16-diene (I), 3β-hydroxy-17-(5-pyrimidyl)androsta-5,16-diene and 17-(1H-benzimidazol-1-yl)androsta-4,16-dien-3-one (II), with IC50 values of 300, 500 and 915 nM, resp. Compds. I, II, the pyrazine compd. and pyrimidine compd. were effective at preventing binding of 3H-R1881 (methyltrienolone, a stable synthetic androgen) to both the mutant LNCaP AR and the wild-type AR, but with a 2.2- to 5-fold higher binding efficiency to the latter. Compds. I and II were also shown to be potent pure AR antagonists. The cell growth studies showed that I and II inhibit the growth of DHT-stimulated LNCaP and LAPC4 prostate cancer cells with IC50 values in the low micromolar range (i.e., <10 μM). Their inhibitory potencies were comparable to that of casodex but remarkably superior to that of flutamide. The pharmacokinetics of compds. I and II in mice were investigated. Following s.c. administration of 50 mg/kg of I and II, peak plasma levels of 16.82 and 5.15 ng/mL, resp., occurred after 30 to 60 min, both compds. were cleared rapidly from plasma (terminal half-lives of 44.17 and 39.93 min, resp.), and neither was detectable at 8 h. Remarkably, compd. I was rapidly converted into a metabolite

tentatively identified as 17-(1H-benzimidazol-1-yl)androsta-3-one.
When tested in vivo, I proved to be very effective at inhibiting the growth of androgen-dependent LAPC4 human prostate tumor xenograft, while II was ineffective. Compd. I (50 mg/kg/twice daily) resulted in a 93.8% redn. (P = 0.00065) in the mean final tumor vol. compared with controls, and it was also significantly more effective than castration. To our knowledge, this is the first example of an antihormonal agent (an inhibitor of androgen synthesis (CYP17 inhibitor)/antiandrogen) that is significantly more effective than castration in suppression of androgen-dependent prostate tumor growth. In view of these impressive anticancer properties, compd. I is a strong candidate for development for the treatment of human prostate cancer.



I

Answer 5:

Bibliographic Information

In vivo preservation of steroid specificity in CWR22 xenografts having a mutated androgen receptor. Shao, Tsang C.; Li, Huiling; Eid, Wael; Ittmann, Michael; Unni, Emmanual; Cunningham, Glenn R. Department of Medicine, VA Medical Center and Baylor College of Medicine, Houston, TX, USA. Prostate (New York, NY, United States) (2003), 57(1), 1-7. Publisher: Wiley-Liss, Inc., CODEN: PRSTDS ISSN: 0270-4137. Journal written in English. CAN 139:394031 AN 2003:780434 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

In vitro studies of CWR22 tumor cells lack steroid specificity. We sought to det. if CWR22 xenografts also lack steroid specificity. We injected castrated nude mice with CWR22 tumor cells (6 × 106 cells) and implanted Alzet osmotic pumps that delivered approx. 1 mg steroid/kg body wt./day. Serum PSA levels were detectable in intact mice and castrated mice treated with testosterone (T), but not in those treated with estradiol (E2), progesterone (P), or flutamide (F). T maintained mean tumor wt. similar to that in intact mice (P = NS). We obsd. no tumors in castrated mice or mice treated with E2, P, or F, and tumor histol. was consistent with wts. The mutation of the androgen receptor (H874Y) that occurs in the CWR22 xenograft model of human prostate cancer does not significantly affect in vivo steroid specificity for E2, P, or F.

Answer 6:

Bibliographic Information

Anti-tumour effects and pharmacokinetic profile of 17-(5'-isoxazolyl)androsta-4,16-dien-3-one (L-39) in mice an inhibitor of androgen synthesis. Nnane, I. P.; Long, B. J.; Ling, Y-Z.; Grigoryev, D. N.; Brodie, A. M. Department of Pharmacology and Experimental Therapeutics, University of Maryland School of Medicine, Baltimore, MD, USA. British Journal of Cancer (2000), 83(1), 74-82. Publisher: Harcourt Publishers Ltd., CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 133:344252 AN 2000:497340 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

17-(5'-Isoxazolyl)androsta-4,16-dien-3-one (L-39), a novel androstene deriv., was synthesized and evaluated in vitro and in vivo. L-39 showed potent and non-competitive inhibition of human testicular microsomal 17α-hydroxylase/C17,20-lyase with an IC50 value of 59 nM and Ki of 22 nM. L-39 also showed potent and competitive inhibition of 5α-reductase in human prostatic microsomes with IC50 and Ki values of 33 and 28 nM resp. L-39 (5 μm) was also shown to manifest anti-androgenic activity in cultures of human prostate cancer cell lines (LNCaP) by preventing the labeled synthetic androgen R1881 (5 nm) from binding to the androgen receptors. Androgen-dependent human prostate cancer xenografts (PC-82) were grown in nude mice and the effects of L-39 (50 mg kg-1 day-1) on tumor growth and prostate-specific antigen (PSA) levels were detd. after 28 days. L-39 diminished tumor growth and wet wts. to a similar extent as castration or flutamide treatment. L-39 also reduced serum PSA levels by more than 80% in the mice bearing human prostate cancer xenografts. Pharmacokinetic studies were also conducted in male Balb/c mice. After s.c. administration of a single bolus dose, L-39 was rapidly absorbed into the systemic circulation. Peak blood plasma levels occurred at 0.75 h and then declined with a t1/2 of 1.51 h. The bioavailability of L-39 after s.c. administration was 28.5%. These results demonstrate that L-39 is a potent inhibitor of androgen synthesis and is effective in reducing the growth of human prostate cancer xenografts in nude mice. Although improvements in the bioavailability are necessary, L-39 is a potential lead compd. with this profile as an inhibitor of prostate cancer growth.

Answer 7:

Bibliographic Information

Effects of new 17α-hydroxylase/C17,20-lyase inhibitors on LNCaP prostate cancer cell growth in vitro and in vivo. Grigoryev, D. N.; Long, B. J.; Nnane, I. P.; Njar, V. C. O.; Liu, Y.; Brodie, A. M. H. Department of Pharmacology and Experimental Therapeutics, University of Maryland, School of Medicine, Baltimore, MD, USA. British Journal of Cancer (1999), 81(4), 622-630. Publisher: Churchill Livingstone, CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 132:189820 AN 1999:700980 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Our lab. has been developing new inhibitors of a key regulatory enzyme of testicular and adrenal androgen synthesis 17α-hydroxylase/C17,20-lyase (P450c17), with the aim of improving prostate cancer treatment. We designed and evaluated two groups of azolyl steroids: Δ5-non-competitive inhibitors (Δ5NCIs), VN/63-1, VN/85-1, VN/87-1 and their corresponding Δ4 derivs. (Δ4NCIs), VN/107-1, VN/108-1 and VN/109-1. The human P450c17 gene was transfected into LNCaP human prostate cancer cells, and the resultant LNCaP-CYP17 cells were utilized to evaluate the inhibitory potency of the new azolyl steroids. VN/85-1 and VN/108-1 had the lowest IC50 values of 1.25±0.44 nM and 2.96±0.78 nM resp., which are much lower than that of the known P 450 inhibitor ketoconazole (80.7±1.8 nM). To det. whether the compds. had direct actions on proliferation of wild-type LNCaP cells, cell growth studies were performed. All of the Δ5NCIs and VN/108-1 blocked the growth-stimulating effects of androgens. In steroid-free media, the Δ5NCIs decreased the proliferation of LNCaP cells by 35-40%, while all of the Δ4NCIs stimulated LNCaP cells growth 1.5- to 2-fold. In androgen receptor (AR) binding studies, carried out to det. the mechanism of this effect, all of the Δ4NCIs (5 μM) displaced 77-82% of synthetic androgen R1881 (5 nM) from the LNCaP AR. The anti-androgen flutamide and the Δ5NCIs displaced 53% and 32-51% of R1881 bound to AR resp. These results suggested that the Δ5NCIs may also be acting as anti-androgens. We further evaluated our inhibitors in male severe combined immunodeficient mice bearing LNCaP tumor xenografts. In this model VN/85-1 was as effective as finasteride at inhibiting tumor growth (26% and 28% inhibition, resp.) and the inhibitory effect of VN/87-1 was similar to that of castration (33% and 36% inhibition resp.). These results suggest that VN/85-1 and VN/87-1 may be potential candidates for treatment of prostate cancer.

Answer 8:

Bibliographic Information

A functional model of adult human prostate epithelium: the role of androgens and stroma in architectural organization and the maintenance of differentiated secretory function. Hayward, Simon W.; Del Buono, Raffaele; Deshpande, Nagesh; Hall, Peter A. Lab. Metab. Stud. Cancer, Imp. Cancer Res. Fund, London, UK. Journal of Cell Science (1992), 102(2), 361-72.

CODEN: JNCSAI ISSN: 0021-9533. Journal written in English. CAN 117:124890 AN 1992:524890 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A functional model of adult human prostate epithelium shows that stromal cells, but not androgenic stimuli, are required for architectural organization of this epithelium. Within an organized structure, androgenic stimulation is required for the establishment of secretory epithelial cell morphol. and assocd. function. In the absence of stromal cells but in the presence of androgens, architectural organization and secretory function are lost. Epithelial parenchymal units (organoids) from human prostate tissue were isolated, cultured within a three-dimensional collagen matrix, and xenografted s.c. into athymic mouse hosts. The grafted gels were rapidly invaded by host fibroblasts. Epithelial organization initially disappeared but was re-established concurrently with the stromal cell invasion. In intact male hosts, cuboidal and columnar cells that expressed human prostate-specific secretory markers were found. In castrated male and in female hosts, epithelial structures were lined with flattened epithelium with no secretory function. This phenomenon could be reversibly replicated by treating intact male hosts with the anti-androgen Flutamide. Gels contg. organoids grafted within 0.45 μm Millipore chambers were not invaded by stromal cells and rapidly lost all epithelial organization and secretory function. When organoids cocultured with human foreskin fibroblasts were grafted within chambers, structural organization of the epithelium was supported. These results indicate that both heterologous human fibroblasts and mouse stromal cells are capable of permissively supporting adult human prostate epithelial function.

Answer 9:

Bibliographic Information

Evaluation of Win 49,596, a novel steroidal androgen receptor antagonist, in animal models of prostate cancer. Juniewicz, Paul E.; Fetrow, N.; Marinelli, J.; Wolf, M.; Young, E.; Lamb, J.; Isaacs, J. T. Dep. Oncopharmacol., Sterling Res. Group, Rensselaer, NY, USA. Prostate (New York, NY, United States) (1991), 18(2), 105-15. CODEN: PRSTDS ISSN: 0270-4137. Journal written in English. CAN 115:127504 AN 1991:527504 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A series of expts. were conducted to evaluate the effects of Win 49,596, a novel steroidal androgen receptor antagonist, in animal models of prostate cancer. In the 1st expt., oral administration of Win 49,596 at doses of 30, 100, or 300 mg/kg/day for 28 days inhibited the growth of the androgen-sensitive PAP variant of the Dunning R-3327 prostatic carcinoma in intact male rats relative to intact controls. The degree of inhibition at 100 and 300 mg/kg/day Win 49,596 was similar to that obsd. in castrate controls as well as in intact rats administered the nonsteroidal androgen receptor antagonist flutamide orally at 15 mg/kg/day. Castration as well as treatment with either Win 49,596 or flutamide also decreased the wt. of the prostate in tumor-bearing animals. Addnl. studies were conducted to det. the effect of Win 49,596 on the growth of the androgen-dependent PC-82 human prostatic carcinoma xenografted into athymic nude male mice. Oral administration of Win 49,596 at 30, 100, or 300 mg/kg/day for 35 days inhibited tumor growth relative to intact controls. The degree of tumor inhibition was similar to that obsd. in intact male mice administered the nonsteroidal androgen receptor antagonist flutamide orally at 30 mg/kg/day but was less than that obsd. following castration. Ventral prostate wts. were also reduced in castrate mice as well as in intact mice administered either Win 49,596 or flutamide. In the last expt., at equiv. total daily dosages of either 150 or 300 mg/kg/day Win 49,596, twice a day (BID) dosing was more effective than once a day (SID) dosing in inhibiting tumor growth. The inhibitory effects of Win 49,596 at 150 mg/kg BID on tumor growth were similar to those obsd. following castration. Although Win 49,596 treatment reduced ventral prostate wts. relative to intact controls, there was no difference between SID vs. BID dosing.

Based on the results of these studies and subject to further testing, Win 49,596 may have utility in the treatment of hormonally-dependent metastatic prostate cancer in humans.

Answer 10:

Bibliographic Information

Androgen manipulation alters oxidative DNA adduct levels in androgen-sensitive prostate cancer cells grown in vitro and in vivo. Pathak Sanjeev; Singh Rajinder; Verschoyle Richard D; Greaves Peter; Farmer Peter B; Steward William P; Mellon J Kilian; Gescher Andreas J; Sharma Ricky A Cancer Biomarkers and Prevention Group, Department of Cancer Studies and Molecular Medicine, University of Leicester, Leicester LE2 7LX, UK Cancer letters (2008), 261(1), 74-83. Journal code: 7600053. ISSN:0304-3835. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 18096312 AN 2008220956 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Intracellular reactive oxygen species (ROS) may cause oxidative DNA damage, resulting in the formation of adducts such as 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxo-dG) and the cyclic pyrimidopurinone N-1, N(2) malondialdehyde-2'-deoxyguanosine (M(1)dG). These adducts have been associated with carcinogenesis, genomic instability and clonal evolution. We tested two hypotheses in human prostate cancer cells grown in vitro and in a xenograft model: (1) treatment of androgen-sensitive cells with DHT increases levels of oxidative DNA adduct levels; (2) flutamide, a competitive androgen receptor antagonist, prevents DHT-induced changes. Levels of M(1)dG and 8-oxo-dG adducts were determined by immunoslot blot and liquid chromatography-tandem mass spectrometry. M(1)dG and 8-oxo-dG levels were significantly higher than control levels in LNCaP cells exposed to supra-physiological concentrations (25-100 nM) of DHT (both $P<0.05$ by ANOVA). Flutamide pre-treatment completely prevented this increase. In the xenograft model, tumour levels of M(1)dG were decreased by 46% ($P=0.001$ by Mann-Whitney Test) in flutamide-treated animals compared to controls. The changes demonstrated suggest that oxidative DNA adducts may serve as biomarkers of the efficacy of androgen manipulation in chemoprevention trials.

Answer 11:

Bibliographic Information

Imaging androgen receptor function during flutamide treatment in the LAPC9 xenograft model. Ilagan Romyla; Zhang Liquin Joann; Pottratz Jill; Le Kim; Salas Sussan; Iyer Meera; Wu Lily; Gambhir Sanjiv S; Carey Michael Department of Biological Chemistry, School of Medicine, University of California at Los Angeles, 10833 Le Conte Avenue, CHS 33-142, Los Angeles, California 90095-1737, USA. milagan@ucla.edu Molecular cancer therapeutics (2005), 4(11), 1662-9. Journal code: 101132535. ISSN:1535-7163. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 16275987 AN 2005596916 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The current understanding of the response of androgen receptor to pharmacologic inhibitors in prostate cancer is derived primarily from serum prostate-specific antigen (PSA) levels. In this study, we test whether a novel androgen receptor-specific molecular imaging system is able to detect the action of the antiandrogen flutamide on androgen receptor function in xenograft models of prostate cancer. Adenoviruses bearing an optical imaging cassette containing an androgen receptor-responsive two-step transcriptional amplification system were injected into androgen-dependent and hormone-refractory tumors of animals undergoing systemic time-controlled release of the antiandrogen flutamide. Imaging of tumors with a cooled charge-coupled device camera revealed that the response of AdTSTA to flutamide is more sensitive and robust than serum PSA measurements. Flutamide inhibits the androgen signaling pathway in androgen-dependent but not refractory tumors. Analysis of androgen receptor and RNA polymerase II binding to the endogenous PSA gene by chromatin immunoprecipitation revealed that flutamide treatment and androgen withdrawal have different molecular mechanisms. The application of imaging technology to study animal models of cancer provides mechanistic insight into antiandrogen targeting of androgen receptor during disease progression.

Answer 12:

Bibliographic Information

Androgen receptor modifications in prostate cancer cells upon long-termandrogen ablation and antiandrogen treatment. Marques Rute B; Erkens-Schulze Sigrun; de Ridder Corrina M; Hermans Karin G; Waltering Kati; Visakorpi Tapio; Trapman Jan; Romijn Johannes C; van Weerden Wytske M; Jenster Guido Department of Urology, Josephine Nefkens Institute, Erasmus Medical Center, Rotterdam, the Netherlands International journal of cancer. Journal international du cancer (2005), 117(2), 221-9. Journal code: 0042124. ISSN:0020-7136. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 15900601 AN 2005458769 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

To study the mechanisms whereby androgen-dependent tumors relapse in patients undergoing androgen blockade, we developed a novel progression model for prostate cancer. The PC346C cell line, established from a transurethral resection of a primary tumor, expresses wild-type (wt) androgen receptor (AR) and secretes prostate-specific antigen (PSA). Optimal proliferation of PC346C requires androgens and is inhibited by the antiandrogen hydroxyflutamide. Orthotopic injection in the dorsal-lateral prostate of castrated athymic nude mice did not produce tumors, whereas fast tumor growth occurred in sham-operated males. Three androgen-independent sublines were derived from PC346C upon long-term in vitro androgen deprivation: PC346DCC, PC346Flu1 and PC346Flu2. PC346DCC exhibited androgen-insensitive growth, which was not inhibited by flutamide. AR and PSA were detected at very low levels, coinciding with background AR activity in a reporter assay, which suggests that these cells have bypassed the AR pathway. PC346Flu1 and PC346Flu2 were derived by culture in steroid-stripped medium supplemented with hydroxyflutamide. PC346Flu1 strongly upregulated AR expression and showed 10-fold higher AR activation than the parental PC346C. PC346Flu1 proliferation was inhibited in vitro by R1881 at 0.1 nM concentration, consistent with a slower tumor growth rate in intact males than in castrated mice. PC346Flu2 carries the well-known T877A AR mutation, causing the receptor to become activated by diverse nonandrogenic ligands including hydroxyflutamide. Array-based comparative genomic hybridization revealed little change between the various PC346 lines. The common alterations include gain of chromosomes 1, 7 and 8q and loss of 13q, which are frequently found in prostate cancer. In conclusion, by in vitro hormone manipulations of a unique androgen-dependent cell line expressing wtAR, we successfully reproduced common AR modifications observed in hormone-refractory prostate cancer: downregulation, overexpression and mutation.

Answer 13:

Bibliographic Information

Membrane androgen receptor activation induces apoptotic regression of human prostate cancer cells in vitro and in vivo. Hatzoglou Anastassia; Kampa Marilena; Kogia Christina; Charalampopoulos Ioannis; Theodoropoulos Panayiotis A; Anezinis Ploutarchos; Dambaki Constantina; Papakonstanti Evangelia A; Stathopoulos Efstathios N; Stournaras Christos; Gravanis Achille; Castanas Elias Laboratory of Experimental Endocrinology, University of Crete School of Medicine, P.O. Box 2208, Heraklion GR-71003, Greece The Journal of clinical endocrinology and metabolism (2005), 90(2), 893-903. Journal code: 0375362. ISSN:0021-972X. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 15585562 AN 2005069390 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Nongenomic androgen actions imply mechanisms different from the classical intracellular androgen receptor (iAR) activation. We have recently reported the identification of a membrane androgen receptor (mAR) on LNCaP human prostate cancer cells, mediating testosterone signal transduction within minutes. In the present study we provide evidence that activation of mAR by nonpermeable, BSA-coupled testosterone results in 1) inhibition of LNCaP cell growth (with a 50% inhibitory concentration of 5.08 nM, similar to the affinity of testosterone for membrane sites); 2) induction in LNCaP cells of both apoptosis and the proapoptotic Fas protein; and 3) a significant decrease in migration, adhesion, and invasion of iAR-negative DU145 human prostate cancer cells. These actions persisted in the presence of antiandrogen flutamide or after decreasing the content of iAR in LNCaP cells by iAR antisense oligonucleotides. Testosterone-BSA was also effective in inducing apoptosis of DU145 human prostate cancer cells, negative for iAR, but expressing mAR

sites. In LNCaP cell-inoculated nude mice, treatment with testosterone-BSA (4.8 mg/kg body weight) for 1 month resulted in a 60% reduction of tumor size compared with that in control animals receiving only BSA, an effect that was not affected by the antiandrogen flutamide. Our findings suggest that activators of mAR may represent a new class of antitumoral agents of prostate cancer.

Answer 14:

Bibliographic Information

Functional domain and motif analyses of androgen receptor coregulator ARA70 and its differential expression in prostate cancer. Hu Yueh-Chiang; Yeh Shuyuan; Yeh Shauh-Der; Sampson Erik R; Huang Jiaoti; Li Peng; Hsu Cheng-Lung; Ting Huei-Ju; Lin Hui-Kuan; Wang Liang; Kim Eungseok; Ni Jing; Chang Chawnshang George Whipple Laboratory for Cancer Research, Department of Pathology, University of Rochester, Rochester, New York 14642, USA The Journal of biological chemistry (2004), 279(32), 33438-46. Journal code: 2985121R. ISSN:0021-9258. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 15166229 AN 2004382634 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Androgen receptor (AR)-associated coregulator 70 (ARA70) was the first identified AR coregulator. However, its molecular mechanism and biological relevance to prostate cancer remain unclear. Here we show that ARA70 interacts with and promotes AR activity via the consensus FXXLF motif within the ARA70-N2 domain (amino acids 176-401). However, it does not promote AR activity via the classic LXXLL motif located at amino acids 92-96, although this classic LXXLL motif is important for ARA70 to interact with other receptors, such as PPARgamma. The molecular mechanisms by which ARA70 enhances AR transactivation involve the increase of AR expression, protein stability, and nuclear translocation. Furthermore, ARA70 protein is more frequently detected in prostate cancer specimens (91.74%) than in benign tissues (64.64%, $p < 0.0001$). ARA70 expression is also increased in high-grade prostate cancer tissues as well as the hormone-refractory LNCaP xenografts and prostate cancer cell lines. Because ARA70 can promote the antiandrogen hydroxyflutamide (HF)-enhanced AR transactivation, the increased ARA70 expression in hormone-refractory prostate tumors may confer the development of HF withdrawal syndrome, commonly diagnosed in patients with the later stages of prostate cancer. Because ARA70-N2 containing the AR-interacting FXXLF motif without coactivation function can suppress HF-enhanced AR transactivation in the hormone-refractory LNCaP cells, using the ARA70-N2 inhibitory peptide at the hormone refractory stage to battle the HF withdrawal syndrome may become an alternative strategy to treat prostate cancer.

Answer 15:

Bibliographic Information

Modulation of androgen receptor transactivation by gelsolin: a newly identified androgen receptor coregulator. Nishimura Kazuo; Ting Huei-Ju; Harada Yasunori; Tokizane Takashi; Nonomura Norio; Kang Hong-Yo; Chang Hong-Chiang; Yeh Shuyuan; Miyamoto Hiroshi; Shin Masaru; Aozasa Katsuyuki; Okuyama Akihiko; Chang Chawnshang Department of Urology, Graduate School of Medicine, Osaka University, Yamadaoka, Suita 565-0871, Japan Cancer research (2003), 63(16), 4888-94. Journal code: 2984705R. ISSN:0008-5472. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 12941811 AN 2003404231 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The partial agonist effect of antiandrogens has been well documented, and such effect is amplified by derived mutant androgen receptors (ARs) in prostate cancer cells. Here we report the identification of gelsolin (GSN) as an

AR-associated protein. Hydroxyflutamide (HF), as well as androgens, can promote the interaction between AR and GSN in a dose-dependent manner. GSN interacts with AR DNA-binding domain and ligand-binding domain via its COOH-terminal domain. Immunolocalization studies show that GSN interacts with AR during nuclear translocation. Functional analyses additionally demonstrate that GSN enhances AR activity in the presence of either androgen or HF. Two peptides representing partial regions of the AR DNA-binding domain and the ligand-binding domain can block the GSN-enhanced AR activity. The expression of GSN is enhanced in LNCaP cells, LNCaP xenografts, and human prostate tumors after androgen depletion. Increasing expression of GSN enhances the AR activity in the presence of HF. Together, these data suggest that the weak androgenic effect of HF may be amplified by increasing the amount of GSN after androgen ablation treatment. Therefore, blockage of the interaction between AR and GSN could become a potential therapeutic target for the treatment of prostate cancer.

Answer 16:

Bibliographic Information

Novel mutations of androgen receptor: a possible mechanism of bicalutamide withdrawal syndrome. Hara Takahito; Miyazaki Jun-ichi; Araki Hideo; Yamaoka Masuo; Kanzaki Naoyuki; Kusaka Masami; Miyamoto Masaomi Pharmaceutical Research Laboratories, Takeda Chemical Industries, Ltd., Osaka 532-8686, Japan. Hara_Takahito@takedo.co.jp Cancer research (2003), 63(1), 149-53. Journal code: 2984705R. ISSN:0008-5472. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 12517791 AN 2003011315 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Most prostate cancers (PCs) become resistant to combined androgen blockade therapy with surgical or medical castration and antiandrogens after several years. Some of these refractory PCs regress after discontinuation of antiandrogen administration [antiandrogen withdrawal syndrome (AWS)]. Although the molecular mechanisms of the AWS are not fully understood because of the lack of suitable experimental models, one hypothesis of the mechanism is mutation of androgen receptor (AR). However, bicalutamide, which has become the most prevalent pure antiandrogen, does not work as an agonist for any mutant AR detected thus far in PC. To elucidate the mechanisms of the AWS, we established and characterized novel LNCaP cell sublines, LNCaP-cxDs, which were generated in vitro by culturing androgen-dependent LNCaP-FGC human PC cells in androgen-depleted medium with bicalutamide to mimic the combined androgen blockade therapy. LNCaP-FGC cells did not grow at first, but they started to grow after 6-13 weeks of culture. Bicalutamide stimulated LNCaP-cxD cell growth and increased prostate-specific antigen secretion from LNCaP-cxD cells both in vitro and in vivo. Sequencing of AR transcripts revealed that the AR in LNCaP-cxD cells harbors a novel mutation in codon 741, TGG (tryptophan) to TGT (cysteine; W741C), or in codon 741, TGG to TTG (leucine; W741L), in the ligand-binding domain. Transactivation assays showed that bicalutamide worked as an agonist for both W741C and W741L mutant ARs. Importantly, another antiandrogen, hydroxyflutamide, worked as an antagonist for these mutant ARs. In summary, we demonstrate for the first time that within only 6-13 weeks of in vitro exposure to bicalutamide, LNCaP-FGC cells, whose growth had initially been suppressed, came to use bicalutamide as an AR agonist via W741 AR mutation to survive.

Our data strongly support the hypothesis that AR mutation is one possible mechanism of the AWS and suggest that flutamide might be effective as a second-line therapy for refractory PC previously treated with bicalutamide.

Answer 17:

Bibliographic Information

Use of the probasin promoter ARR2PB to express Bax in androgen receptor-positive prostate cancer cells. Andriani F; Nan B; Yu J; Li X; Weigel N L; McPhaul M J; Kasper S; Kagawa S; Fang B; Matusik R J; Denner L; Marcelli M Department of Medicine, Baylor College of Medicine, and VA Medical Center, Houston, TX 77030, USA Journal of the National Cancer Institute (2001), 93(17), 1314-24. Journal code: 7503089. ISSN:0027-8874. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T); (RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 11535706 AN 2001493280 MEDLINE

Abstract

BACKGROUND: Adenovirus-mediated overexpression of the apoptosis-inducing protein Bax can induce apoptosis in prostate cancer cell lines. Constitutive overexpression of Bax could result in unwanted apoptosis in every site of accidental Bax accumulation in vivo. Therefore, we developed an adenoviral construct (Av-ARR2PB-Bax) in which the probasin promoter, modified to contain two androgen response elements, drives Bax expression. This promoter would be expected to limit expression of Bax to cells expressing the androgen receptor. METHODS: A variety of androgen receptor (AR)-positive and -negative cell lines of prostatic or nonprostatic origin were infected with Av-ARR2PB-Bax or a control virus, Av-ARR2PB-CAT, in which the same promoter drives expression of the chloramphenicol acetyl transferase-reporter gene. Bax expression and apoptosis in vitro were assessed by western blot analysis. Tumor size and apoptosis in vivo were assessed after four weekly injections of Av-ARR2PB-Bax or Av-ARR2PB-CAT into subcutaneous LNCaP xenografts growing in uncastrated male mice. All statistical tests were two-sided. RESULTS: Bax was overexpressed in an androgen-dependent way in AR-positive cell lines of prostatic origin but not in AR-positive cells of nonprostatic origin or in AR-negative cell lines of either prostatic or nonprostatic origin. The androgen dihydrotestosterone activated apoptosis in LNCaP cells infected with Av-ARR2PB-Bax but not in those infected with Av-ARR2PB-CAT. Av-ARR2PB-Bax-injected LNCaP xenograft tumors decreased in tumor size from 34.1 mm3 (95% confidence interval [CI] = 25.1 mm3 to 43.1 mm3) to 24.6 mm3 (95% CI = -2.5 mm3 to 51.7 mm3), but the difference was not statistically significant (P =.5). Tumors injected with Av-ARR2PB-CAT increased in size, from 28.9 mm3 (95% CI = 12.7 mm3 to 45.1 mm3) to 206 mm3 (95% CI = 122 mm3 to 290 mm3) (P =.002) and contained statistically significant more apoptotic cells (23.3% [95% CI = 21.1% to 25.6%] versus 9.5% [95% CI = 8.0% to 11.1]) (P<.001).

CONCLUSIONS: Av-ARR2PB-Bax induces androgen-dependent therapeutic apoptosis in vitro and in vivo by activating apoptosis in AR-positive cells derived specifically from prostatic epithelium and does not affect nonprostatic cells.

Answer 18:

Bibliographic Information

New topical antiandrogenic formulations can stimulate hair growth in human bald scalp grafted onto mice. Sintov A; Serafimovich S; Gilhar A Ben-Gurion University of the Negev, The Institutes for Applied Research, PO Box 653, Beer-Sheva, Israel. asintov@bgumail.bgu.ac.il International journal of pharmaceutics (2000), 194(1), 125-34. Journal code: 7804127. ISSN:0378-5173. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 10601691 AN 2000070724 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The purpose of this study was to test the ability of topical formulations of finasteride and flutamide to re-enlarge hair follicles in male-pattern baldness. This was evaluated by an experimental model of human scalp skin graft transplanted onto SCID mice. A comparison was made between formulations containing finasteride and flutamide, and a vehicle formulation in terms of the mean hairs per graft, length, diameter of the shafts, and structures of the growth stages of the hair. Flutamide and finasteride had a significantly higher effect (P<0.05) than the placebo in all the tested parameters, but flutamide demonstrated more hair per graft and longer hair shafts than finasteride (P<0.05). The number of hairs per graft for flutamide and finasteride groups were 1.22+/-0. 47 and 0.88+/-0.95 hairs/0.5 mm2 graft, respectively, versus 0. 35+/-0.6 hairs/graft for vehicle-treated graft. Similarly, hair lengths for flutamide and finasteride were 5.82+/-0.50 and 4.50+/-0. 32 mm, respectively, versus 2.83+/-0.18 mm for the vehicle-treated grafts. An in vitro diffusion study of flutamide gel using hairless mouse skin demonstrated the beneficial effect of the vehicle composition in comparison with a hydroalcoholic solution or a gel containing no penetration enhancer. It is therefore suggested that this topical composition containing flutamide or finasteride may effectively result in regression of male-pattern baldness.